REMARKS

Claims 1-20 are pending. New claims 21-42 are added herein and claims 1-20 are deleted herein without prejudice. The specification is amended as set out above and as previously amended in the parent application, U.S. Patent Application 08/739,703.

Applicants request that line 36 of page 38 be corrected to improve the legibility of the phrase "avoids inhibition by pre-existing antibodies in human blood." Applicants also request correction of several typographical errors: on page 19, line 1, "caboxy" is replace with "carboxy"; on page 28, line 31, "Conjuqates" is replaced with "Conjugates" ; on page 29, line 4, "desireable" is replaced with "desirable"; on page 39, line 21, "singe" is replaced with "single"; on page 46, line 19, "resultd" is replaced with "resulted"; on page 53, line 23, "reatments" is replaced with "treatments"; on page 56, line 29, "tanscription-translation" is replaced with "transcription/translation"; on page 64, line 3, sepecificity" is replaced with "specificity"; on page 64, line 28, "sequenc" is replaced with "sequence"; on page 64, line 33, "dwonstream" is replaced with "downstream"; on page 64, line 35, "full-lenth" is replaced with "full-length"; and, on page 67, line 6 "herin" is replace by "herein."

Applicants also request that the linker be correctly identified on page 42, line 29 and page 49, line 14 as "$(Gly_4Ser)_3$," as supported by the correct designation on page 56, line 14. The Brief Description of the Drawings is also amended to refer to Figures 2 A, 2B, and 2C, Figures 3A and 3B, and Figures 8A and 8B. The description of Figure 2 has been further amended to clarify that 2B shows the inhibition of toxicity by anti-DT goat serum and that 2C shows the inhibition of toxicity by anti-DT human serum. Support for this clarification is found in the title for Table 4, page 47, which refers to "[i]nhibition of UCHT1-CRM9 toxicity by serum;" on page

48, lines 4-5, which refers to "the mechanism by which serum inhibits toxicity;" on page 48, lines 7-8, which refers to "anti-DT" in reference to human and goat sera. The description of Figure 2 was also amended to specify that the goat and human sera were each incubated with DT mutants. The amendment is supported on page 48, lines 7-9, which makes clear that the serum was either goat or human. Thus, no new matter is believed to be added by the above amendments.

The Sequence Listing is also amended so that it complies with the requirements of 37 CFR §§ 1.821 through 1.825. A new computer readable form for the Sequence Listing in full is provided on disk. No new matter is believed to be added by amendment of the Sequence Listing as support for the additional sequences is found in Table 6. Specifically, the sequences disclosed in Table 6 are provided as SEQ ID NO:7 through SEQ ID NO:14.

Table 6 is replaced in order to identify the SEQ ID NOs and to clarify the use of parentheses around nucleotides in SEQ ID NO:8 and SEQ ID NO:11. Specifically, the expository text of Table 6 has been amended to indicate that the primers listed as SEQ ID NO:8 and SEQ ID NO:11 consist of a mixture of the sequence without the nucleotide(s) in parentheses and the sequence (s) with the nucleotide(s) in paretheses replacing the immediately preceding nucleotide(s). This amendment is inherent to the use of the parentheses in the table as filed; thus, no new matter is believed to be added.

New claim 21 provides a fusion immunotoxin comprising a single chain variable region of an anti-CD3antibody linked to a toxin moiety. Support for the fusion immunotoxin comprising a toxin moiety and an antibody moiety is present in claims 1 and 3 as originally filed and throughout the specification. Support for the single chain variable region anti-CD3 moiety is

found in Example 9, pages 38-53. Claim 22 further provides that the toxin moiety is a diphtheria toxin moiety, and support for this is found in claim 1 as originally filed and throughout the specification.

Claim 23 provides the fusion immunotoxin having a diphtheria toxin moiety which is a mutant of native diphtheria toxin that retains toxicity but has reduced binding to non-target cells. Support for this claim can be found on page 9, lines 21-25. Claim 24 specifies that the diphtheria toxin moiety is a truncation of native diphtheria toxin, and claim 25 further specifies that the truncation is at the carboxy terminus. Support for these claims can be found at page 13, lines13-14; page 40, lines 28-32. Support for claim 26, which provides a fusion immunotoxin having a DT390 truncated diphtheria moiety, can be found at page 9, lines 15-16; page 13, lines 13-15; and Example 9, pages 38-54.

Claims 27 and 28 provides the fusion immunotoxin, wherein the single chain variable region of the anti-CD3 antibody comprises or consists of the variable light domain linked to the variable heavy domain, optionally via a linker. Support for these claims can be found in claim 4 as originally filed and in the specification at Examples 9 and 10, including, for example, page 41, lines 27-31; page 49, line 14; page 56, line15; and page 58, line 28 through page 59, line 6.

Claim 29 provides the fusion immunotoxin wherein the anti-CD3 antibody moiety binds to the CD3ϵ epitope. The specification gives support for the anti-CD3ϵ property of the antibody moiety on page 49, line 13.

Claim 30 specifies the immunotoxin, wherein the anti-CD3 antibody is UCHT1. Support for this claim can be found throughout the specification including, for example,

throughout Example 10. Claim 31 further specifies that the toxin antibody of the immunotoxin comprising UCHT1 is DT390. Support for this claim can be found in claim 8 as originally filed and throughout the specification. See, for example, page 9, line 18.

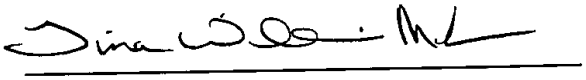
Claim 32 provides the fusion immunotoxin comprising DT390 linked via its C terminus, optionally via a linker, to the single chain variable region of anti-CD3 antibody. Claim 33 further provides this orientation of the fusion immunotoxin the variable light domain linked at its carboxy terminus to the variable heavy domain, optionally via a linker. Claim 35 further specifies that the fusion immunotoxin comprises DT390 linked via its carboxy terminus, optionally via a linker, to the variable light domain of an anti-CD3 antibody, and the variable light domain linked via its carboxy terminus, optionally via a linker, to the variable heavy domain of the anti-CD3 antibody. Claims 34 and 36 further provide these specific orientations with UCHT1 as the anti-CD3 antibody, and claim 37 specifically provides a fusion immunotoxin consisting of DT390 linked via its carboxy terminus through a linker to the variable light domain of UCHT1 which is linked via its carboxy terminus through linker $(Gly_4Ser)_3$. Support for various orientations of the toxin and single chain variable region can be found at page 66, lines 20-24. Figures 13 and 15 show a schematic with a truncated toxin moiety linked at its C-terminus to a single chain variable region, specifically the variable light (V_L) domain, which is in turn linked at its C-terminus to the variable heavy (V_H) domain. Furthermore, Figure 17 shows the construct for a single chain immunotoxin comprising DT390 linked at its C-terminus to the sFv region of an anti-CD3 antibody. The figure legend for Figure 17, at page 7, indicates that this orientation can be used with a UCHT1 variable region. Specific support for the variable light (V_L) region linked at its C-terminus to the variable heavy (V_H) region is also provided at page 58, line 28 through page 59, line 6. Furthermore, specific support for the $(Gly_4Ser)_3$ linker can be found on page 41, lines 19-31, as amended above, and page 56, lines 10-25.

Claims 38-42 provide methods of treatment using the immunotoxin of the present invention. Specifically, claim 38 provides a method of inhibiting rejection of a transplanted tissue or organ, claim 39 provides a method of treating an autoimmune disease, claim 40 provides a method of treating T cell leukemias or lymphomas, claim 41 provides a method of treating graft-versus-host disease, and claim 42 provides a method of treating acquired immunodeficiency syndrome. Support for these claims can be found in claims 9,12, 15, and 18, as originally filed and throughout the specification, including, for example, page 40, lines 3-7.

No new matter is believed to be added by any of the preceding amendments. Thus, consideration and allowance of the pending application are respectfully requested. The Examiner is invited to contact the undersigned counsel by telephone if such contact would expedite prosecution.

A check in the amount of $36.00 is enclosed to cover the cost of 2 additional claims over the cancelled 20 claims. No additional fees are believed to be due; however, the Commissioner is hereby authorized to change any additional fees that may be required or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,



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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner of Patents, Washington, D.C. 20231, on the date indicated below.

Tina Williams McKeon

April 12, 2000
Date

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